(19) KOREAN INTELLECTUAL PROPERTY OFFICE

KOREAN PATENT ABSTRACTS

(11)Publication number: 1020010055736 A
(43)Date of publication of application: 04.07.2001

(21)Application number: 1019990057020
(22)Date of filing: 13.12.1999
(30)Priority: ..

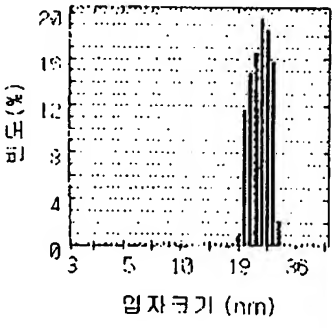
(51)Int. Cl A61K 9/107

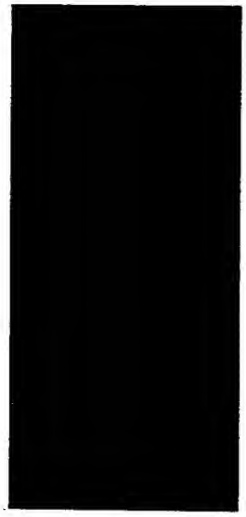
(71)Applicant: FDL, INC.
(72)Inventor: HONG, JI UNG
JI, SANG CHEOL
LEE, GYU HYEON
PARK, EUN SEOK

(54) MICROEMULSION INJECTION COMPOSITION OF PROPOFOL

(57) Abstract:

PURPOSE: A micro emulsion injection composition of propofol obtained by using Solutol 15^TH as a non-ionic surfactant and an auxiliary solvent or auxiliary surfactant is provided, which is useful as an injection of general anesthesia having no side effects by microorganism contamination and lipid overload caused by bean oil used in conventional emulsions. CONSTITUTION: The micro emulsion injection composition of propofol for general anesthesia is obtained by adding 1 to 50% by weight of an auxiliary solvent or an auxiliary surfactant to 0.1 to 10.0% by weight of propofol as an emulsion and 0.1 to 20.0% by weight of polyethylene glycol 660 12-hydroxystearate as a non-ionic surfactant based on the total weight of the composition. The composition can be used with conventional antiseptic, stabilizer, buffer solution and tonicity adjustment agent.





COPYRIGHT 2001 KIPO

Legal Status

Date of request for an examination (00000000)

Notification date of refusal decision ( )

Final disposal of an application (withrawal)

Korean Patent Publication
No. 10-2001-0055736

Propofol microemulsion injection composition

BACKGROUND

The present disclosure relates to a propofol microemulsion injection composition which is useful as an induction and maintenance agent for general anesthesia, and more particularly to a propofol microemulsion injection composition for general anesthesia injection, which does not have adverse side effects induced by bacterial contamination and lipid overload produced by soybean oil used in the conventional technology, and allows for mass production by dissolving poorly soluble propofol in the oil phase and adding the nonionic surfactant polyethylene glycol 660 12-hydroxy stearate (Solutol HS 15™, BASF, Germany) and a co-solvent or co-surfactant to prepare a propofol microemulsion injection composition.

Propofol, with its chemical name of 2,6-diisopropylphenol, is a drug used for the purpose of induction and maintenance for general anesthesia, and is known as an effective drug which provides rapid anesthetic action by easily passing through the blood-brain barrier and acting on the central nervous system during the intravenous injection due to its high lipophilicity.

However, propofol is a colorless and clear oil phase material with its solubility in water of about 147 μg/mℓ (Trapan, Int. J. Pharm., 139, 215-8, 1996), which is so low that the water-immiscible material should be emulsified or dissolved by an appropriate method for administration as an injection.

Adjuvants used in preparing a drug having a low solubility should

have the following: ability to emulsify or dissolve an amount of an active ingredient enough to provide its efficacy; no toxicities and adverse side effects; and physical and chemical stability after admixture with the effective ingredient.

In an effort to develop a propofol injection conventionally, a method for dissolving propofol including using Cremophor EL™ (BASF) as a solubilizing agent, mixing propofol alone or in combination with a solvent such as an optimal amount of ethyl oleate, castor oil, etc., and mixing the solution with Cremophor EL™ and ethanol, polyethylene glycol, propylene glycol, etc. as a co-solvent has been developed (US Patent No. 4798846). However, Cremophor EL™ as a solubilizing agent has adverse side effects to facilitate the excessive secretion of histamine *in vivo*, leading to hypersensitivity reactions (Briggs *et al.*, Br. J. Anaesth., 1981, 53, 1197-1202).

In WO/1997/010814, an attempt to disperse propofol by using polysorbate 80 was made. However, polysorbate 80 also has problems that histamine secretion *in vivo* is facilitated, leading to hypersensitivity reactions (Masini, Agents Actions, 16, 470-7, 1985).

Due to adverse side effects by the surfactant, the only propofol injection currently on the market is an emulsion which contains soybean oil, phosphatide, and glycerin (US Patent Nos. 5714520 and 5908869). The soybean oil used in propofol emulsion induces rapid bacterial proliferation, and it has been reported that operations by using propofol cause cases of fever, sepsis, etc. (Bennett et al., Postoperative Infections, 333, 147-154, 1994).

It has also been reported that when anesthesia is maintained with propofol emulsion for a long time, the excessive soybean oil administered together with the emulsion induces adverse side effects such as hyperlipidemia, rapid increase in levels of bilirubin in the blood, liver damage, immune dysfunction, etc. which are related to lipid overload (Eddlestone *et al.*, Intensive Care Med., 17, 424-426, 1991). Moreover, because propofol emulsion has an opaque appearance as an emulsion characteristic, care should be taken to prevent impurities, which are almost impossible to detect, from being incorporated when equipment is used or ampoules are opened.

In methods for preparing emulsions, expensive equipment such as a high-pressure homogenizer or a microfluidizer is generally used. Despite the expensive equipment, there are problems in homogeneity and storage stability of oil droplets according to kind of equipment used and operating conditions. When oil droplet sizes in emulsion are not homogeneous, the storage stability is deteriorated. In particular, it has been reported that when there are large particles in size of about 4 ㎛ to about 6 ㎛, intravenous injection may cause emboli in the blood vessels of lung, liver, kidney, brain, etc. (Fugita et al., Eur. Surg. Res., 3, 436-453, 1971).

As a method patent to produce a propofol emulsion which is more homogeneous in oil droplet distribution and more improved in storage stability than the conventional products, disclosed are a method for maintaining an operation under predetermined conditions of about 40,000 psi to about 45,000 psi by using a high-pressure homogenizer (Korea Patent Application No. 96-43799) and a method for homogenizing particles at conditions of about

5,000 psi to about 23,000 psi by using a microfluidizer (Korea Patent Application No. 93-26876).

Since the concept of microemulsion was first discovered by a British chemist Schulman in 1943, much research has been conducted to apply it as a medical product. Microemulsions are a kind of emulsion, transparent unlike emulsions, and a thermodynamically stable formula which contains fine particles in size of about 100 ㎚ or less. In particular, microemulsions are economical because they are spontaneously formed by stirring or mixing without any difficulties such as operations of special equipment such as a high-pressure homogenizer or a microfluidizer under predetermined conditions. In addition, microemulsions maintain constant particle sizes without any coacervation, are good in homogeneity of particles, and excellent in storage stability.

SUMMARY

In order to solve problems of the conventional art, the present invention provides a propofol microemulsion injection composition for general anesthesia injection without any adverse side effects by bacterial contamination and lipid overload produced by soybean oil as the problems that the conventional art has by using Solutol HS 15™ and a co-solvent or co-surfactant to prepare a propofol microemulsion injection composition.

Further, the present invention provides a propofol injection composition which is economical because a thermodynamically stable microemulsion is formed simply by stirring or mixing without operating expensive equipment under predetermined conditions, and allows for mass production.

Furthermore, the present invention provides a propofol microemulsion injection composition for general anesthesia injection which is safer than the technology using the conventional Cremophor EL™ or polysorbate 80, since impurities derived from a used equipment are easy to detect due to its transparent properties, the incorporation of the impurities *in vivo* are prevented, and a non-ionic surfactant Solutol HS 15™ with less adverse side effects such as hypersensitivity reactions is used.

The present invention is characterized in a propofol microemulsion injection composition for general anesthesia injection formed by dissolving propofol in oil, and adding Solutol HS 15™ (which has less adverse side effects) as a nonionic surfactant, and a suitable co-solvent or co-surfactant, and then, simply stirring or mixing the solution.

Solutol HS 15™ is a polyethylene glycol 660 12-hydroxy stearate produced by reacting 12-hydroxy stearic acid with ethylene oxide. Acute toxicity experiments (LD_{50}) on mice for 7 days showed that Solutol HS 15™ ($\geq$ 3.16 g/kg (Technical Literature, 1997, BASF) is much safer than Cremophor EL™ ($\geq$ 2.5 g/kg (Technical Literature, 1988, BASF) when intravenously injected. In particular, it has been reported that Solutol HS 15™ is less than Cremophor EL™ by several 10-folds at the same concentration in terms of histamine release responsible for hypersensitivity reactions when injected (Lorenz *et al.*, Agents and Actions, 12, 64-80, 1982).

Thus, the present inventors suitably used Solutol HS 15™ and a

co-solvent or co-surfactant to prepare a poropofol injection, discovered that the injection has advantages over the conventional emulsion product in that there are no adverse side effects by bacterial contamination and hyperlipidemia due to the use of soybean oil, mass production is economically possible without using expensive equipment under predetermined conditions, and adverse side effects may be prevented because the injection's transparent properties make impurities such as bits of glass easy to detect and the propofol microemulsion injection composition causes less hypersensitivity reactions than the conventional technology using Cremophor EL™ or polysorbate 80, and made the present invention.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a graph illustrating droplet sizes measured by dynamic light scattering in Example 1 according to the present invention.

Fig. 2 is a graph illustrating droplet sizes measured by dynamic light scattering in Example 5 according to the present invention.

DETAILED DESCRIPTION OF THE EMBODIMENTS

Reference will now be made in detail to the embodiments of the present disclosure, examples of which are illustrated in the accompanying drawings.

Hereinafter, the present invention will be described in more detail.

The injection composition according to the present invention is a propofol microemulsion injection composition for general anesthesia injection which simply forms a microemulsion by

dissolving propofol in an appropriate ratio of Solutol HS 15™ and a co-solvent or co-surfactant and stirring or mixing the solution when water is added. Preferably, the concentration of propofol is about 0.1wt% to about 10wt%, the content of Solutol HS 15™, a surfactant, is about 0.1wt% to about 20.0wt%, and the content of a co-solvent or co-surfactant is about 0.5wt% to about 50.0wt%, based on a total content of the composition.

When the content of Solutol HS 15™ is about 0.1wt% or less, propofol, an active ingredient, is not fully solubilized. When the content is about 20.0wt% or more, there are adverse side effects in use for a long time.

A co-solvent or co-surfactant useful in the present invention may comprise at least one selected from the group consisting of a lower alcohol such as ethanol and benzyl alcohol, a fatty acid such as glycerin, polyethylene glycol, propylene glycol, N-methylpyrrolidone, 2-pyrrolidone, and capric acid, and any ester thereof. When the concentration of the co-solvent or co-surfactant is about 1wt% or less, microemulsion is not formed.

When the content is about 50wt% or more, adverse side effects such as pain or hemolysis may be induced during the injection (Krzyzaniak et al., Int. J. Pharm., 152, 193-200, 1997).

In the present invention, a conventional preservative, a stabilizer, a buffer, and an isotonic agent may be added so as to prepare a propofol microemulsion injection composition.

The propofol microemulsion injection composition for general anesthesia injection according to the present invention may be

directly injected in the form of a final product, but may be diluted in a physiological saline solution and a dextrose injection.

Hereinafter, the present invention will be described in more detail with reference to Examples, but is not limited thereto.

According to Examples 1 to 5, propofol microemulsion injection compositions for general anesthesia injection were prepared as follows.

Example 1

Propofol	1.0 g
Solutol HS 15™	5.0 g
Ethanol	5.0 g
Distilled water for injection	proper quantity
Total volume	100 ㎖

5.0 g of ethanol was added to 5.0 g of Solutol HS 15™ and then, homogenously mixed. The mixture was dissolved in 1.0 g of propofol. A microemulsion was prepared while distilled water for injection was slowly added to make up a total volume of 100 ㎖. The resulting microemulsion injection composition was autoclaved at 121℃ for 15 min using an autoclave (Model No. Mac-5100, Eyela Co.).

Example 2

Propofol	0.1 g
Solutol HS 15™	1.0 g
Polyethylene glycol 300	2.0 g
1/15 M phosphate buffer (pH 7.5)	proper quantity

Total volume	100 ㎖

2.0 g of polyethylene glycol 300 was added to 1.0 g of Solutol HS 15™, and then, heated to 40℃ and homogenously mixed. The mixture was dissolved in 0.1 g of propofol and cooled to room temperature. A microemulsion was prepared while 1/15 M phosphate buffer (pH 7.5) was slowly added to make up a total volume of 100 ㎖. The resulting microemulsion injection composition was autoclaved at 121℃ for 15 min using an autoclave.

Example 3

Propofol	2.0 g
Solutol HS 15™	5.0 g
Propylene glycol	10.0 g
Sodium hydrogen sulfite	0.1 g
Distilled water for injection	proper quantity
Total volume	100 ㎖

10.0 g of polyethylene glycol was added to 5.0 g of Solutol HS 15™ and homogenously mixed. The mixture was dissolved in 2.0 g of propofol. 50 ㎖ of distilled water for injection was slowly added to the solution, which was later dissolved in 0.1 g of sodium hydrogen sulfite. Finally, a microemulsion was prepared in a total volume of 100 ㎖ using distilled water for injection. The resulting microemulsion injection composition was autoclaved at 121℃ for 15 min using an autoclave.

Example 4

Propofol	5.0 g
Solutol HS 15™	15.0 g
Glycerin	10.0 g

Distilled water for injection	proper quantity
Total volume	100 ㎖

10.0 g of glycerin was added to 15.0 g of Solutol HS 15™, heated to 40℃, and homogenously mixed. The mixture was dissolved in 5.0 g of propofol and cooled to room temperature. A microemulsion was prepared while distilled water for injection was slowly added to make up a total volume of 100 ㎖. The resulting microemulsion injection composition was autoclaved at 121℃ for 15 min using an autoclave.

Example 5

Propofol	10.0 g
Solutol HS 15™	20.0 g
N-methylpyrrolidone	30.0 g
Distilled water for injection	proper quantity
Total volume	100 ㎖

30.0 g of N-methylpyrrolidone was added to 20.0 g of Solutol HS 15™, heated to 40℃, and homogenously mixed. The mixture was dissolved in 10.0 g of propofol and cooled to room temperature. A microemulsion was prepared while distilled water for injection was slowly added to make up a total volume of 100 ㎖. The resulting microemulsion injection composition was autoclaved at 121℃ for 15 min using an autoclave.

A conventional product (10 ㎖ of 1% Diprivan, Zeneca Korea) was purchased to measure a particle distribution as in Comparative Example 1.

Comparative Example 1

The conventional product (10 of 1% Diprivan) was an emulsion which is comprised of protocol at 10 mg/mℓ, soybean oil at 100 mg/mℓ, phospholipid at 12 mg/mℓ, and glycerin at 22.5 mg/mℓ. The oil droplet size of the purchased conventional product was measured by using a light scattering spectrophotometer (Model No. LPA-3100, Otsuka Electronics).

A comparison between an oil droplet distribution result of the conventional product measured by dynamic light scattering and that disclosed in WO 1997/010814 is shown in table 1.

Table 1. Oil droplet distribution results of the conventional product (1% Diprivan)

(Unit: nm)

	Comparative Example 1	WO 1997/010814
Average particle size	252.1 ± 106[1)]	123.8 ± 37.9[1)]
Maximal particle size	5167.8[1)]	>10,000(1,342)[2)]

[1)] Measurement results by dynamic light scattering

[2)] A measurement result by an A3 particle counter VS, the number of particles per mℓ in parenthesis.

The result in Comparative Example 1, in which the oil droplet distribution of the conventional product was measured by dynamic light scattering, had a very broad distribution from 95 nm to 5000 nm or more. Considering that a significant measurement range of an apparatus (Light scattering spectrophotometer, Model No. LPA-3100, Otsuka Electronics) used in the experiment was 3 nm

to 5000 ㎚, it is determined that there were oil droplets of sizes exceeding this range.

According to the measurement result of the conventional product using an A3 particle counter VS in WO 1997/010814, it was revealed that there oil droplets having the size of 10 ㎛ or bigger were 1,300 or more per ㎖. It has been reported that these big oil droplets may make emulsions physically unstable, inducing vascular emboli when the emulsion is injected (Lieberman et al., Pharmaceutical Dosage Forms: Disperse Systems, 2nd Ed., Vol. 2, 269-272, 1996).

In experimental example, droplet sizes in propofol microemusion injection compositions prepared in Examples 1 to 5 were measured.

Experimental Example 1

By using a light scattering spectrophotometer, droplet sizes in propofol microemulsion injection compositions in Examples 1 to 5 were measured immediately after preparing the compositions and after storing the compositions at 40℃ for 1 month. The results were shown in Table 2, and Figs. 1 and 2.

The droplet sizes in propofol microemulsion injection compositions in Examples 1 to 5 were 100 ㎚ or less, which were smaller than those in the conventional emulsion product. The distribution range of the droplets was so narrow that the droplets can be seen to have been homogenously formed. In particular, it was shown that droplet sizes measured after storing the compositions at 40℃ for 1 month were also stable without any change, as in those measured immediately after manufacture.

Table 2. Droplet sizes in propofol microemulsion injection compositions

(Unit: nm)

	Immediately after manufacture	1 month after acceleration experiments
Example 1	21.0 ± 2	21.2 ± 6
Example 2	22.8 ± 2	23.1 ± 5
Example 3	23.6 ± 3	23.4 ± 4
Example 4	18.5 ± 5	18.2 ± 9
Example 5	24.0 ± 10	24.1 ± 7

Figs. 1 and 2 are graphs measuring droplet size distributions of Examples 1 and 5, respectively, immediately after manufacture by dynamic light scattering using a light scattering spectrophotometer.

Embodiments provide a propofol microemulsion injection composition without any adverse side effects by bacterial contamination and lipid overload produced by soybean oil that the conventional product uses by using the nonionic surfactant Solutol HS 15™ and a co-solvent or co-surfactant to prepare a propofol microemulsion injection composition.

Embodiments allow for economical mass production because microemulsion may be formed simply by stirring or mixing without using any expensive equipment. Because the propofol microemulsion injection composition of the present invention has transparent properties and impurities derived from the equipment used are easy to detect, risks of impurities introduction *in vivo* may be prevented.

Furthermore, a propofol microemulsion injection composition which the present invention provides by using Solutol HS 15™ with less adverse side effects is safer than the conventional product using Cremophor EL™ or polysorbate 80.

Although embodiments have been described with reference to a number of illustrative embodiments thereof, it should be understood that numerous other modifications and embodiments can be devised by those skilled in the art that will fall within the spirit and scope of the principles of this disclosure. More particularly, various variations and modifications are possible in the component parts and/or arrangements of the subject combination arrangement within the scope of the disclosure, the drawings and the appended claims. In addition to variations and modifications in the component parts and/or arrangements, alternative uses will also be apparent to those skilled in the art.

What is claimed is:

1. A propofol microemulsion injection composition, comprising:

propofol dissolved in oil;

polyethylene glycol 660 12-hydroxy stearate as a non-ionic surfactant; and

a co-solvent or a co-surfactant.

2. The composition according to claim 1, wherein propofol is about 0.1wt% to about 10.0wt% based on a total content of the composition.

3. The composition according to claim 1, wherein polyethylene glycol 660 12-hydroxy stearate is about 0.1wt% to about 20wt% based on a total content of the composition.

4. The composition according to claim 1, wherein the co-solvent or co-surfactant is about 1wt% to about 50wt% based on a total content of the composition.

5. The composition according to claim 1, wherein the co-solvent or co-surfactant is at least one selected from the group consisting of a lower alcohol such as ethanol and benzyl alcohol, a fatty acid such as glycerin, polyethylene glycol, propylene glycol, N-methylpyrrolidone, 2-pyrrolidone and capric acid, and ester thereof.

6. The composition according to any one of claims 1 to 5, wherein the composition comprises a conventional preservative, a stabilizer, a buffer, and an isotonic agent.